Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Clinical Classification of Obesity and Implications for Metabolic Dysfunction-Associated Fatty Liver Disease and Treatment

Yuping Ding[1,2], Quanjun Deng[1,2], Mei Yang[1,2], Haiyan Niu[1,2], Zuoyu Wang[1,2], Shihai Xia[1,2]

[1]Department of Gastroenterology and Hepatology, Characteristic Medical Center of the Chinese People's Armed Police Force, Tianjin, 300162, People's Republic of China; [2]Tianjin Key Laboratory of Hepatopancreatic Fibrosis and Molecular Diagnosis & Treatment, Tianjin, 300162, People's Republic of China

Correspondence: Shihai Xia, Department of Gastroenterology and Hepatology, Characteristic Medical Center of the Chinese People's Armed Police Force; Tianjin Key Laboratory of Hepatopancreatic Fibrosis and Molecular Diagnosis & Treatment, 220, Chenglin Road, Dongli, Tianjin, 300162, People's Republic of China, Email xshhcx@sina.com

Abstract: Obesity,and metabolic dysfunction-associated fatty liver disease (MAFLD) have reached epidemic proportions globally. Obesity and MAFLD frequently coexist and act synergistically to increase the risk of adverse clinical outcomes (both hepatic and extrahepatic). Type 2 diabetes mellitus (T2DM) is the most important risk factor for rapid progression of steatohepatitis and advanced fibrosis. Conversely, the later stages of MAFLD are associated with an increased risk of T2DM incident. According to the proposed criteria, MAFLD is diagnosed in patients with liver steatosis and in at least one in three: overweight or obese, T2DM, or signs of metabolic dysregulation if they are of normal weight. However, the clinical classification and correlation between obesity and MAFLD is more complex than expected. In addition, treatment for obesity and MAFLD are associated with a reduced risk of T2DM, suggesting that liver-based treatments could reduce the risk of developing T2DM. This review describes the clinical classification of obesity and MAFLD, discusses the clinical features of various types of obesity and MAFLD, emphasizes the role of visceral obesity and insulin resistance (IR) in the development of MAFLD,and summarizes the existing treatments for obesity and MAFLD that reduce the risk of developing T2DM.

Keywords: obesity, metabolic dysfunction-associated fatty liver disease, phenotypes, type 2 diabetes mellitus, treatment, weight loss

Introduction

Obesity is defined as excessive accumulation or improper distribution of body fat (BF).[1] Other concomitant illnesses include type 2 diabetes mellitus (T2DM), hepatic steatosis, cardiovascular disease,[2,3] stroke, dyslipidemia, and hypertension, making obesity treatment more essential.[4] Conventional classifications of overweight and obesity have been developed based on the Body Mass Index (BMI) and ethnicity-specific thresholds. Adults with a BMI of 25 to 29.9 kg/m^2 were categorized as overweight, those with a BMI of 30 kg/m^2 as obese, and those with a BMI of 18.5 to 24.9 kg/m^2 as normal (ie, lean) weight.[5] For Asian populations, BMI from 23.0 to 24.9 kg/m^2 is considered overweight, BMI ≥25.0 kg/m^2 is considered obese, and 18. 5–22. 9 kg/m^2 were regarded as normal weight.[6] The most reported adult subtypes of obesity and heterogeneity used for research were as follows: (i) normal-weight obesity (NWO) syndrome; (ii) metabolically obese normal weight (MONW); metabolically unhealthy normal-weight (MUHNW); (iii) metabolically healthy obesity (MHO); (iv) metabolically unhealthy obesity (MUO), metabolically obese (MO), metabolically abnormal obese (MAO), (v) sarcopenic obesity (SO).[7]

In the past several decades, the prevalence of obesity has increased nearly three times, reaching epidemic levels. According to the World Health Organization(WHO), more than 650 million adults, or over 13% of the world's population, had this chronic illness in 2016.[8] According to previous reports,[9] up to 463 million individuals globally and 1 in 11 adults have TD2M.[10] Patients with non-alcoholic fatty liver disease (NAFLD) may have a higher risk of developing diabetes because they often exhibit aberrant glucose metabolism, which is indicative of T2DM and is characterized by elevated blood glucose levels,

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insulin resistance(IR), and impaired islet cell function.[11] The prevalence rates of NAFLD and non-alcoholic steatohepatitis (NASH) in T2DM were 65.04% and 31.55%, respectively, according to a meta-analysis of 156 studies[12] including 1,832,125 individuals. Clinically significant fibrosis (F2-F4) was observed in 35.54% of the patients with T2DM and NAFLD, whereas advanced fibrosis (F3-F4) was present in 14.95% of these patients.

Obese patients frequently have “fatty liver.” A global panel of experts redefined fatty liver disease in 2020 from a negative state, excluding diagnosis, to a positive state of fatty liver disease coupled with metabolic dysfunction.[13] Clinical Practice Guidelines for the Diagnosis and Management of Metabolically Related Fatty Liver Diseases issued by the Asian Pacific Association for the Study of the Liver (APASL) were adopted as a new consensus suggestion.[14] While the American Society of Liver Disease (AASLD) and the European Association for the Study of Liver Diseases (EASL) have not yet approved the nomenclature change from metabolic dysfunction-associated fatty liver disease(MAFLD) to NAFLD. The current proposal to rename NAFLD as metabolic dysfunction-associated steatosis liver disease(MASLD)is the result of the recent multinational Delphi consensus.[15] As previously described, NAFLD and MAFLD have a noticeable overlap[13,16,17] and based on a Cohen kappa value of up to 0.92, the two definitions have a high level of overall concordance.[18] Furthermore, a meta-analysis based on information from[19] research covering 1,088,677 individuals globally revealed that the prevalence of MAFLD was comparable to that of NAFLD. Only 4.0% of NAFLD patients fail to fulfill the new MAFLD diagnostic standards.[19] MAFLD represents the vast majority of NAFLD to some extent; therefore, in our review, previous NAFLD studies were also included in the analysis of MAFLD.

A recent systematic review and meta-analysis[20] of MAFLD prevalence in an Asian context, comprising 13,044,518 individuals, suggested that the prevalence of MAFLD in this region was 29.62%. Another 29 studies[21] comprising 6,095 individuals reported that MAFLD prevalence in overweight or obese children and adolescents from the general population was 33.78%, regardless of diagnostic techniques. One meta[22] identified 116 relevant studies comprising 2,667,052 participants in the general population with an estimated global MAFLD prevalence of 51.3% among overweight/obese adults using ultrasound diagnostic technique, and the generating prevalence rate of males (59.0%) had a significantly higher MAFLD prevalence than females (47.5%).

Steatosis, steatohepatitis, and accompanying fibrosis can be used as pathological lesion forms of MAFLD, such as metabolic associated steatohepatitis (MASH),[23,24] MAFLD with significant fibrosis,[25] and MAFLD associated with advanced liver fibrosis.[26] It arises in the setting of poor metabolic status, such as being overweight or obese, and is linked to lipid manipulation and abnormalities in glucose homeostasis. MAFLD is part of a complex, multi-organic set of disorders, rather than merely a liver condition.[27] It is fueled by intricate gene-environment interactions, creating a dysfunctional metabolic medium with a range of outcomes.[28] Based on the proposed criteria, MAFLD is diagnosed when patients with hepatic steatosis meet one or more of the following three criteria: Overweight or obese, T2DM, or signs of metabolic dysregulation (Increased waist circumference, high blood pressure, low HDL cholesterol levels, hypertriglyceridemia, impaired fasting plasma glucose, IR, and chronic subclinical inflammation are at least two of the risk factors.)[13,14] This leads us to believe that there are three different types of MAFLD: I, MALFD with obesity or overweight; II, normal weight MAFLD (Lean MAFLD, both hepatic steatosis and evidence of metabolic dysregulation must be present); and III, MAFLD with T2DM.

The categorization of MAFLD and metabolic phenotypes of obesity are closely associated [Figure 1], and the proper classification of obesity facilitates the diagnosis and categorization of metabolic fatty liver disease and gives more insight into the MAFLD treatment strategy. The metabolic phenotypes of obesity [Table 1] and particular MAFLD types [Table 2] are the main focus of this review. The significance of various definitions, clinical characteristics, genes and molecules, phenotypes, prognosis, and other metabolic disorders is of particular note. Here, we highlight some pathomechanisms and assess their clinical utility.

Visceral obesity is the principal contributor to insulin resistance, which is the pathophysiological underpinning of Obesity, MAFLD, and T2DM[2] [Figure 2]. As a result, treating metabolic fatty liver includes treating both IR and obesity, in addition to the liver itself, and weight loss continues to be the cornerstone of MAFLD treatment, as is prompt and adequate treatment. Not only do ideal therapies result in considerable weight loss, hepatic steatosis remission, and fibrosis regression, but they also reduce IR and prevent the onset of T2DM [Table 3]. As a result, alternative treatments are advised.

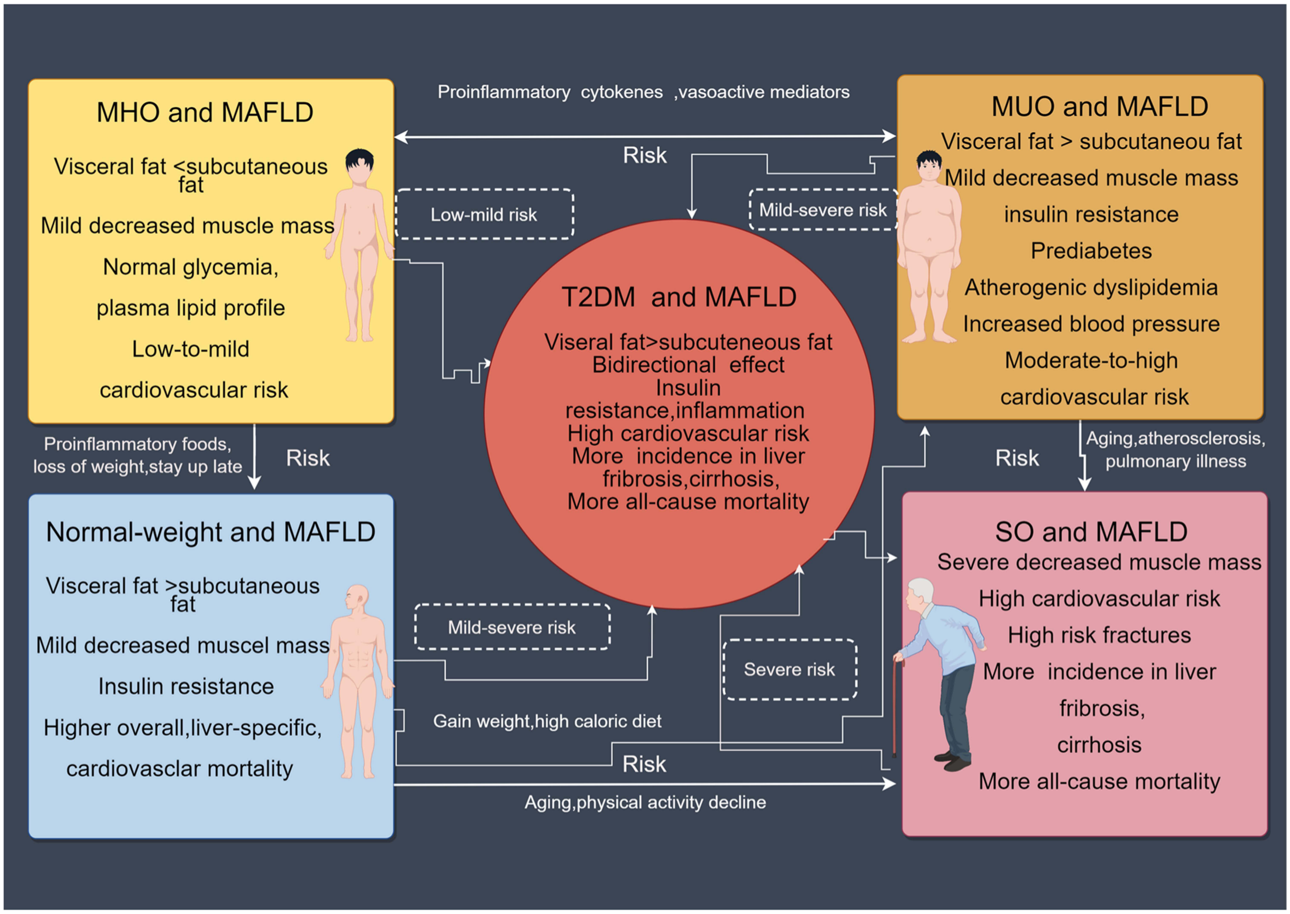

Figure 1 Different forms of metabolic fatty liver disease interchanging with one another. (By Figdraw. ID:AAPSIddcb1).
Abbreviations: MHO, Metabolically healthy obesity; MUO, Metabolically Unhealthy Obese; SO, Sarcopenia-related obesity; MAFLD, Metabolic dysfunction-associated fatty liver disease.

Metabolic Phenotypic Obesity

The diversity of obesity, which includes a wide range of potential causes, is highlighted by the occurrence of several "phenotypes of obesity" with varying metabolic and cardiovascular disease (CVD)risks.[7,31,41,124,125] [Table 1] De Lorenzo et al[126] identified three distinct obesity phenotypes: MHO, NWO, and MUO. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for differentiating between MHO and MUO as well as the International Diabetes Federation (IDF) criteria for the differential diagnosis of NWO syndrome and MONW were used to evaluate metabolic diseases.[127] Particularly, two subclasses of NWO have been identified:[128] normal weight healthy metabolic obesity, typical of normal weight obesity syndrome, with a high CVD risk index,[38] and normal weight obesity associated with metabolic syndrome (MetS) and IR,[129] defined as MONW.[37] In contrast, SO is characterized by a loss of lean mass, BF accumulation, a decline in skeletal muscle mass, and a loss of muscular strength.[75,130]

Normal Weight Obesity (NWO) Syndrome

Individuals with normal weight who have hereditary obesity and are in the early stages of low-grade inflammation are considered to have Normal Weight Obesity (NWO) syndrome.[31] There is a considerable loss of lean mass, equivalent to at least 1.5 kg (FFM kg), especially in the lower limb muscle mass, when the percentage of body fat (PBF) approaches 30%.[29] They exhibit elevated levels of TNF-α, IL-1, and IL-8 as well as oxidative stress caused by metabolic anomalies.[-32] An alteration in a set of genes linked to aging and inflammation was revealed by NWO. Cardiovascular risk scores and fat distribution were strongly correlated in NWO patients.[33] NWO patients had more vascular inflammation than normal

Table 1 Definitions Used for Heterogeneity Subtypes in Obese Individuals

	Definitions	Other Terminology for this Group	Epidemiology	Clinical Characteristics	Pathomechanism Molecular Phenotype	Prognosis
NWO	Loss of lean mass, equivalent to at least 1.5 kg (FFM kg), in the lower limb muscle mass, when the percentage of body fat (PBF) approaches 30%.[29]		The NWO in 23,748 Chinese was 6.6% in women and 9.5% in men[30]	In the early stages of low-grade inflammation[31]	Elevated levels of TNF-α, IL-1, and IL-8[32]	Cardiovascular risk scores and fat distribution are strongly correlated in NWO persons.[33] Increase in MetS and cardiometabolic risk.[30]
MONW	A normal BMI (18.5–25 kg/m^2), and decreased lean mass. Adiposity and ectopic fat distribution are also increased.[34]	MANO, Metabolically Unhealthy Normal-Weight Phenotype (MUHNW)[35]	The type of individual has a higher incidence	Eating too much sugar and not enough grains, fish, or root vegetables; High body fat, and poor metabolic health in people of normal weight.[36] Young and show early symptoms of insulin resistance, hyperinsulinemia, and dyslipidemia, associated with a higher risk of diabetes and cardiovascular disease (CVD).[37]	Adipose tissue is a significant source of proinflammatory cytokines[2] High levels of hsCRP, TNF-α, IL-1, IL-1, IL-6, and IL-8 are seen in the blood.[38,39]	Elderly people with this genotype are more likely to die from CVD-related causes overall.[40]
Metabolically healthy obesity (MHO)	Having a combination of obesity and absence of components of the metabolic syndrome with the exception of normal lipid and blood pressure profiles, good insulin sensitivity, obese with BMI over 30 kg/m^2, and not exhibiting metabolic anomalies.[41,42]	Metabolically normal obese, metabolically benign obese, metabolically healthy overweight/obese	Comprise 6–75% of the obese population.[43–45]	Young, physically active, good eating habits. Liver function, blood pressure is normal, serum lipid profile is stable, level of inflammation is low.[43] Reduced VAT and ectopic fat deposition (including less hepatic steatosis).[41]	Myristic, palmitic, stearic, oleic, and linoleic acids.[46] Healthy levels of HOMA, QUICKI, Mffm/l, hsCRP, and IL-6.[38] Leptin, have increased in MHO people.[47] Pro-inflammatory proteins such as HRP, hsCRP, C4A, and ITIH4 are downregulated while anti-inflammatory molecules such as AHSG, HRG, and RBP4 are overexpressed in MHO.[48]	Still has the danger of developing into the unhealthy phenotype linked to a number of serious chronic illnesses, It shouldn't be regarded as a benign condition.[49]

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The Metabolically Unhealthy Obese Phenotype (MUO)/MAO	BMI greater than 30 kg/m^2 and a body fat percentage greater than 30%.[50]	Metabolically abnormal obesity (MAO)		An ectopic fat distribution and excessive VAT accumulation[51]	Pro-inflammatory cytokines IL-6, IL-8, MCP-1, RANTES, MIP1 and PAI-1 are more incidents of heterogeneous expression seen in VAT[7] Increased levels of hsCRP and TNF-α[52] NLRP3 gene and IL1b is increased in VAT; The genes for ATP binding cassette subfamily G 1 (ABCG1) and carnitine palmitoyltransferase 1A (CPT1A).[53]	Higher risk of mortality due to serious health issues like T2DM and CVD.[51]
Sarcopenic obesity (SO)	A loss of lean mass and an increase in the percentage of fat mass.[54] The subquintile of the skeletal muscle index (skeletal muscle/BMI), along with the measurement of grasping force (30 kg for men and 20 kg for women).[55] Extra body fat that is higher than the median or >27% for men and 38% for women, as well as loss of muscle mass and strength.[56]	Sarcopenic overweight	Kim et al,[57] the prevalence of sarcopenic obesity in patients was 15%	Risk factors such advanced age, a decline in physical activity, atherosclerosis, and pulmonary illness[54]	Increased levels of serum hs-CRP among males[58] Several loci, PTPRD, CDK14, and IMMP2L genes.[7] A rise in TNF-α, IL-6, IL-1, MCP-1, and fetuin-A (FetA)[59] Resistance to leptin.[60,61]	Perna et al[59] a higher risk of fractures, and a worse metabolic pattern.

Abbreviations: SO, Sarcopenia-related obesity; MUO, Metabolically Unhealthy Obese; MAO, Metabolically abnormal obesity; MHO, Metabolically healthy obesity; MONW, Metabolically Obese Normal Weight; NWO, Normal Weight Obesity Syndrome; TNF-α, Tumour Necrosis Factor alpha; IL-1, Interleukin 1; IL-8, Interleukin 8; BMI, Body mass index; MANO, metabolically abnormal with no obesity,

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Table 2 The Types and Subtypes in MAFLD Individuals

Types	Subtypes	Epidemiology	Disease Severity and Prognosis	Risk Factors	Pathophysiology
Overweight or obese and MAFLD	**MHO and MAFLD**	35.5% (96/270) of these obese individuals had NAFLD, 8.2% (22/270) had NASH, and 4.4% (12/270) had liver fibrosis.[62] 45% of MHO persons had ultrasonically-defined MAFLD[63]			
	MUO and MAFLD	90–95% of individuals with extreme obesity and associated MetS characteristics have imaging-defined MAFLD, and more than a third of these patients develop histology NASH.[64]	"Cryptogenic" cirrhosis also frequently exhibit MetS characteristics, "burned-out" NASH may account for the majority of these instances.[65] Proinflammatory and vasoactive mediators that may facilitate the emergence of cardiometabolic problems linked to obesity.[8,66,67]	Presence of expanded and inflamed (dysfunctional) visceral adipose tissue.[68,69] Dietary fructose intake[70] Drinking sweetened drinks[71] Cardio-respiratory fitness[72] Elevated SUA levels.[73] PNPLA3 G/G genotype carriers had a risk of cirrhosis[74]	Visceral adipose tissue differs from subcutaneous fat in that it releases more pro-inflammatory and pro-fibrogenic mediators, has greater lipolytic rates, and is associated with increased insulin resistance[31]
	The SO and MAFLD	Sarcopenia from 12.2% to 43.6% in MAFLD patients.[75] SO was 5.4% (1297 /23,889) in MAFLD patients.[76]	SO were separately linked to a greater risk of NAFLD,[77–79] NASH,[77,78] and severe fibrosis.[77,79]	High-risk SO had significantly higher cumulative incidences of significant liver fibrosis, CVD, cirrhosis, and all-cause mortality.[76]	
Normal-weight and MAFLD (Lean MAFLD)	**MUNW and MAFLD**	Lean MAFLD was shown to be present in 5.1% of the general population and 19.2% of the world's MAFLD population,[80]	Higher overall, liver-specific, and cardiovascular mortality[80] greater all-cause mortality.[81] Experience fewer cardiovascular events and fatalities.[82,83] Reduced rates of metabolic abnormalities, cirrhosis, and cardiovascular disease.[84,85] Lean MAFLD may have a similar prognosis to patients with overweight or obese MAFLD compared to healthy individuals.	Food quality in addition to overall calorie intake.[86] Pro-inflammatory foods or a strong pro-inflammatory profile.[36] More total energy, less fiber, lower levels of antioxidant chemicals, fewer servings of fruit, legumes, nuts, and seeds.[87] Consume more cholesterol[88] Higher dietary inflammatory index scores Microbiota is more enriched than patients with obesity and MAFLD (such as Erysipelotrichaceae and Clostridiales) A decrease in the Marvinbryantia and Christensellenaceae R7 group and an increase in the Dorea spp compared to healthy individuals of normal weight.[89]	The distribution of body fat is likely governed by genetic factors, variants like DCST2 rs905938 and GORAB rs10919388[90,91] L3MBTL3, DNAH10, and CCDC92 were associated with a higher risk of cardiometabolic disease, lower peripheral fat, and increased insulin[92] PNPLA3 risk allele to higher levels of fibrosis and the onset of steatohepatitis.[93,94] TM6SF2 gene showed increased rates of transport of rs58542926 C>T[95,96] Patients IFNL4 TT allele and severe fibrosis (P=0.02)[97]

MAFLD and T2DM		Prevalence of MAFLD in people with T2DM is ~56%[98] Prevalence rates of NAFLD and NASH in T2DM were 65.04% and 31.55%[12]	MAFLD and T2DM patients 35.54% had clinically significant fibrosis (F2-F4), while 14.95% had advanced fibrosis (F3-F4)[12] More MAFLD patients with fibrosis stage 3 than those with fibrosis of stages 0–2 (51% versus 31%) acquired incident T2DM.[99] It's important to notice that a rising amount of steatosis was likewise connected to the T2DM event in MAFLD patients with 0–2 fibrosis.[99]	(PNPLA3, TM6SF2, and other MAFLD-related genetic variations).[28,100,101] Lipid accumulation in the liver Elevated levels of VLDL and small dense LDLs and decreased levels of HDL-cholesterol.[102]	Dietary components (Saturated fat and carbohydrate intake), Changes in gut microbiota; Intestinal function (bile acid metabolism, levels of lipopolysaccharide and incretins, or altered intestinal permeability).[16]

Abbreviations: MetS, Metabolic Syndrome; SO, Sarcopenia-related obesity; SUA, Serum uric acid; T2DM, Type 2 diabetes mellitus; MAFLD, metabolic dysfunction-associated fatty liver disease; IFNL4, Interferon lambda 4 gene; TM6SF2, transmembrane 6 superfamily member 2; PNPLA3, Recombinant Patatin Like Phospholipase Domain Containing Protein 3; VLDL, Very Low Density Lipoproteins; LDL, Low-Density Lipoprotein; L3MBTL3, lethal(3)malignant brain tumor-like protein 3; DNAH10, Ciliary dynein heavy chain 10; CCDC92, Coiled coil domain containing protein 92; DCST2, DC-STAMP domain containing 2; GORAB; RAB6-Interacting Golgin; CVD, Cardiovascular disease.

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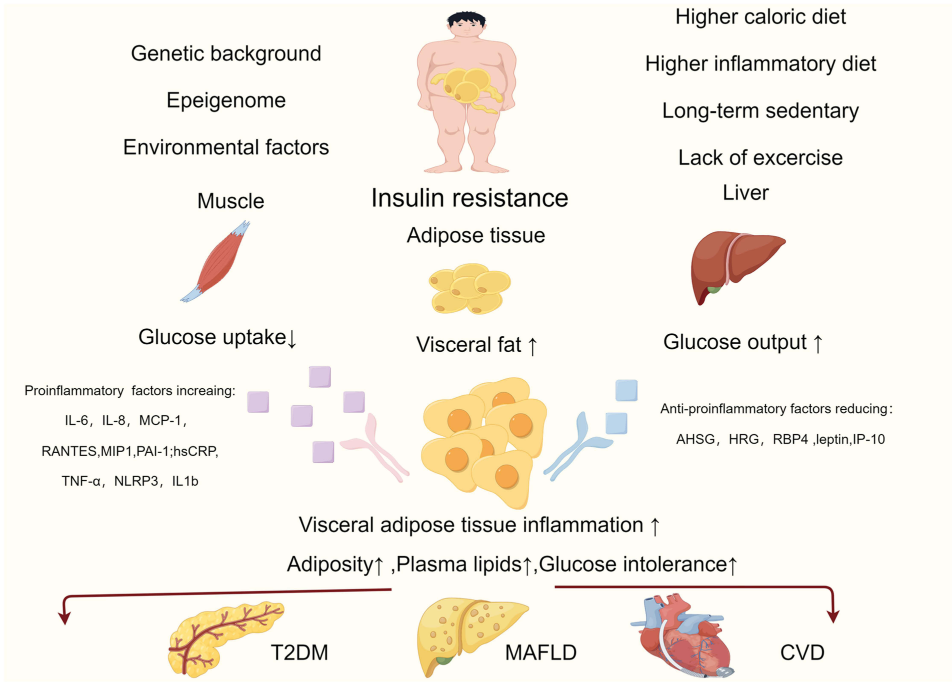

Figure 2 The underlying causes of MAFLD and T2DM include visceral obesity and insulin resistance, and inflammatory factors play a significant role in the onset and progression of the illness. (By Figdraw. ID:IIAPIadaa4).

Abbreviations: T2DM, Type 2 diabetes mellitus; MAFLD,metabolic dysfunction-associated fatty liver disease; CVD, Cardiovascular disease; IL-6, Interleukin 6; IL-8, Interleukin 8; MCP-1, Monocyte chemoattractant protein-1; AHSG, Alpha-2 Heremans Schmid Glycoprotein; HRG, Heregulin; RBP4,retinol-binding protein 4; IP-10, Interferon-gamma (IFN-gamma)-induced protein 10; RANTES, Regulated upon activation normal T cell expressed and presumably secreted; MIP1, Mps1 interacting protein-1; PAI-1, plasminogen activator inhibitor-1; hsCRP, hypersensitive C reactive protein; TNF-α, Tumour Necrosis Factor alpha; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; IL1b, interleukin-1beta.

lean subjects, according to a study by Kang et al.[131] After accounting for the impact of abdominal obesity, the prevalence of NWO in 23,748 Chinese was 6.6% in women and 9.5% in men, and it was linked to an increase in MetS and CVD risk.[30]

Metabolically Obese Normal Weight (MONW)/The Metabolically Unhealthy Normal-Weight Phenotype (MUHNW)

Metabolically Obese Normal Weight (MONW), metabolically abnormal with no obesity (MANO), and metabolically unhealthy normal weight phenotype (MUHNW) are other names for this condition.[35] The phenotype has an elevated Visceral Adipose Tissue (VAT) and abdominal Subcutaneous Adipose Tissue (SAT), a normal BMI (18.5–25 kg/m^2), and decreased lean mass. Adiposity and ectopic fat distribution also increased.[34] Diet quality may be an independent determinant of metabolic health. A study[36] showed that components of dietary intake, such as high intake of sugar and low intake of cereals, fish, and root vegetables, were associated with normal-weight obesity, high body fat percentage, and poor metabolic health.

Individuals with MetS have a higher incidence of clinical features that are frequently identified because they tend to overlook clinical therapy or prevention. They are typically young and exhibit early symptoms of IR, hyperinsulinemia, and dyslipidemia, all of which may be associated with a higher risk of T2DM and CVD.[37] Additionally, elderly individuals with this genotype are more likely to die from CVD-related causes.[40] In obese individuals, adipose tissue is a significant source of pro-inflammatory cytokines,[2] and high levels of hypersensitive C-reactive protein(hsCRP), tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-8 are observed in the blood.[38,39]

Metabolically Healthy Obesity (MHO)

At present, there is no international standard for the identification of MHO, and more than 30 distinct criteria have been used to operationalize symptoms.[132] The MHO has been proposed to have a combination of obesity and absence of

Table 3 Treatments for Obesity and MAFLD, Considering Pathological Processes That are Targets for Therapy

Intervention	Classification	Mechanism	Mean %TBWL	Liver Fat Improvement	NAS improvement/ Indicators of Liver Enzymology	NFS/LS Improvement	INS or T2DM Improvement
Lifestyle Modifications (weight loss)	Calorie-restricted interventions[103]	Calorie-restricted		HS (p < 0.001)[103]	Effects on ALT reduction (p< 0.001)[103]	LS (p= 0.009).	
	Mediterranean diet's macronutrient[104,105]	Impact of the macronutrient profile	No[105]	MED/LC induced a greater %HFC decrease (p= 0.036)[104] Decrease in IHL (%) than LF/HCD (p = 0.03).[105]	Reduced GGT, ALT (p <0.05)[104]; Reduced ALT (p= 0.02)[103]	LS (p= 0.05).[103]	GHb (p <0.05)[104] Decrease in HOMA-IR Insulin concentration decline (p= 0.008)[105]
	Aerobic physical activity	150 minutes each week; more than 10,000 steps per day, more than a year, higher amounts of physical activity- between 200 and 300 minutes per week.[106]	At least weight loss of 7% (usually greater than 10%)[106]				
Antiobesity Pharmacotherapy	Liraglutide 3.0 g	GLP-1 analog inhibits food intake by inducing 51 s[107]	8.0% vs 2.6% after 56 wk[107]	Steatosis improvement 83% vs.45% (p=0.009)[107]	-1.3 change in NAS score and 74% had NAS im- provement. 39% had complete resolution.[107]	-0.2 change in fibrosis (p= 0.11).[107]	-5.18 change in HbA1C (p= 0.03)
	Semaglutide 0.4 mg	Long-acting GLP-1 analog inhibits food intake by inducing satiety[108]	-13 vs.-1% after 72 wk		-59 vs -17% after 72 wk.	43% had an improvement in fibrosis stage in the 0.4-mg group and 33% in the placebo group (p= 0.48).	GHb level among patients with T2DM -1.07 in the 0.2-mg group and -0.01 in the placebo group
	Orlistat	Reversible pancreatic lipase inhibitor, decreasing the hydrolysis of intestinal fat, therefore, absorpt[109]	-8.3 vs.-6% after 36 wk.[109]	LFC-9.1% 24 weeks[110]	No[111]	-0.14 change in fibrosis.[111]	HOMA-IR -1.05; P=0.04[111]

(*Continued*)

Table 3 (Continued).

Intervention	Classification	Mechanism	Mean %TBWL	Liver Fat Improvement	NAS improvement/ Indicators of Liver Enzymology	NFS/LS Improvement	INS or T2DM Improvement
Bariatric Endoscopic Interventions	IGB	Introducing an empty balloon into the stomach through an upper endoscopy. The balloon is inflated with air or saline to reduce the stomach volume. This will result in early satiety and weight loss.[112]	-11.7%after 6 mo.[113] Average reduction in participant body weight of 11.9 kg		90% had 3 points improvement in their NAS.[113] Improvement (p=0.03) in the NAS.[114] 83.5% of patients' NAS scores had improved[115]	1.17 stages improvement in 15% of participants in NFS.[113]	
	ESG	A minimally invasive bariatric procedure that is done through endoscopically inserting a suturing device to remodel the greater curvature Of the stomach.[116]	-14.9% after 6 mo.		4.0 points per year using HSI.[117]	20% had significant improvement in NFS (from F3-F4 indeterminate to F0-F2).[117] 0.3 points annually following the procedure.[117]	
	DMR	By modifying, eliminating, or omitting duodenal exposure to intra-luminal nutrients, favorable metabolic effects were seen.[118]	Three months of DMR decreased by 3.1 kg ($p<0.001$)[119]				HbA1C levels dramatically decreased by 1.72% ($p=0.02$)[119]

Bariatric Surgical Intervention	SG	A restrictive bariatric procedure that involves resection of two-thirds of the Stomach's greater curvature and gastric fundus creating a long tubular gastric conduit running along the lesser curvature.[120]	31.7% after 6 mo.[121] BMI:44. 54±5. 45 kg/m^2 to 34. 23±2. 66 after one year[122]		2.3 NAS score improvement.[121] Falling from 5.2±1.96 to 2.63±1.55 after one year[122]	Significant reduction in NFS of 0.7[121]	
	RYGB	A reconstructive procedure performed by connecting a limb of the small intestine to a small gastric pouch forming a shape of "Y." Bypassing a portion of the large stomach pouch and proximal small intestine reduces the amount of nutrients and calories being absorbed.[123]	34.6% after 6 mo.[121]	Improvement or complete resolution of steatosis, by 91%.[123]	Improvement or complete resolution of steatohepatitis by 60%, y.[123] -2.8 NAS score Improvement[121]	31% improvement in NFS[123] NFS score.-1.0 reduction[121]	

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; NFS, nonalcoholic fatty liver disease fibrosis score; TBWL, total body weight loss; INS, Insulin Resistance; HS, hepatic steatosis; MED/LC, Mediterranean/low-carbohydrate; HFC, hepatic fat content; IHL, In intrahepatic lipid; LS, Liver stiffness; GHb, Glycated hemoglobin; HOMA-IR, Homeostasis model assessment; LF/HCD, low-fat, high-carb diet; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; GLP-1, glucagon-like peptide 1; HbA1C, Hemoglobin A1c; T2DM, type 2 diabetes; LFC, Liver fat content; wk, weeks; IGB, intragastric balloon; mo, months; ESG, Endoscopic sleeve Gastroplasty; HSI, Hepatic steatosis index; DMR, endoscopic duodenal mucosal resurfacing; SG, Sleeve gastrectomy; BMI, Body mass index; RYGB, Roux-en-Y gastric Bypass; y, year.

components of metabolic syndrome (in some definitions with the exception of waist circumference), with the exception of normal lipid and blood pressure profiles, good insulin sensitivity, obesity with BMI over 30 kg/m2, and no metabolic anomalies.[41] Reduced visceral adiposity in relation to high total fat levels may contribute to increased insulin sensitivity and decreased inflammation.[42] MHO are often young, physically active, and have good eating habits. Their livers operated correctly, their blood pressure was normal, their serum lipid profile was stable, and their level of inflammation was low.[43]

According to various classification criteria, the MHO group comprises 6–75% of the obese population.[43–45] Several underlying reasons, including reduced VAT and ectopic fat deposition (including less hepatic steatosis) compared to the more expandable subcutaneous fat depots, have been hypothesized to explain the better profile in those with MHO.[41] Compared to healthy individuals of normal weight, patients with MHO have a higher risk of developing metabolic syndrome.[133] The fatty acid composition of myristic, palmitic, stearic, oleic, and linoleic acids may help explain why MHO has a lower inflammatory state.[46] All MHO patients have a healthy Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index(QUICKI), insulin sensitivity index (ISI) (Mffm/l), hsCRP, and IL-6.[38] Other biomarkers, such as leptin, have increased in MHO patients.[47] Pro-inflammatory proteins such as histamine releasing peptide (HRP), hsCRP, Complement Component 4a (C4A), and inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) are downregulated, while anti-inflammatory molecules such as Alpha-2 Heremans Schmid Glycoprotein (AHSG), Heregulin (HRG), and retinol-binding protein -4(RBP4) are overexpressed in MHO.[48] MHO still has the risk of developing into an unhealthy phenotype and is linked to a number of serious chronic illnesses, such as CVD, hypertension, T2DM, chronic kidney disease, and several types of cancer. Therefore, it should not be regarded as a benign condition.[49]

The Metabolically Unhealthy Obese Phenotype (MUO)/MAO

Metabolically unhealthy obesity (MUO), also known as metabolically abnormal obesity (MAO), is characterized by a BMI greater than 30 kg/m^2 and a body fat percentage greater than 30%.[50] Patients with MUO typically have ectopic fat distribution and excessive VAT accumulation, and they are thought to be at a higher risk of mortality due to serious health issues such as T2DM and CVD.[51] This group differed considerably from the MHO subtype in terms of body fat (%), high-density lipoprotein cholesterol, systolic blood pressure, triglycerides, glucose, and insulin.[134]

Obesity-related inflammation and metabolic problems are exacerbated by macrophage infiltration into adipose tissue, which is a significant pathogenic component.[135,136] Alanine aminotransferase (ALT) is a metabolic syndrome-related biomarker that can be significantly increased. The pro-inflammatory cytokines IL-6, IL-8, Monocyte chemoattractant protein-1 (MCP-1), regulated upon activation normal T cell expressed and presumably secreted(RANTES), Mps1 interacting protein-1 (MIP1), and plasminogen activator inhibitor-1 (PAI-1) are more incidents of heterogeneous expression seen in VAT, whereas leptin and interferon-gamma (IFN-gamma)-induced protein 10 (IP-10) are mostly expressed in SAT.[7] Leucine rich repeat-containing receptor family NACHT, LRR, and PYD domain-containing protein-3 (NLRP3)gene and IL-1b are increased in VAT, which is infiltrated by pro-inflammatory macrophages in the MUO/MAO subgroup. VAT is associated with metabolic problems and its activation and expression are upregulated.[137] Increased levels of hsCRP and TNF-α were linked to higher waist circumference (WC) in males and BMI in women, according to Marques-Vidal et al.[52] The number of genomic alterations that can be connected to various MAO symptoms rises as a result of epigenetic mechanisms, WC and levels of fasting triglycerides are two characteristics of the phenotypic hypertriglycéridaemic-waist (HTGW), for instance. It is believed to be associated with the genes for ATP binding cassette subfamily G 1 (ABCG1) and carnitine palmitoyltransferase 1A (CPT1A).[53]

Sarcopenic Obesity (SO)

Sarcopenic obesity (SO), which is characterized by a loss of lean mass and an increase in the percentage of fat mass, is associated with risk factors such as advanced age, a decline in physical activity, atherosclerosis, and pulmonary illness.[54] Individuals of various ages, not just older adults, can develop SO. According to Kim et al's research,[57] the prevalence of sarcopenic non-obese, sarcopenic, and non-sarcopenic obesity in patients was 10%, 15%, and 20%, respectively. The subquintile of the skeletal muscle index (skeletal muscle/BMI), along with the measurement of grasping force (30 kg for men and 20 kg for women), is frequently used for diagnosis.[55] Perna et al[56] stated that according to dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA), SO refers to those who have extra body fat that is higher than the median or >27% for men and 38% for women, as well as loss of muscle mass and strength. Age-related reductions in muscle mass and strength may then cause a reduction in physical activity in the elderly, which in turn leads to weight gain and an increase in abdominal fat.[138]

Perna et al[59] reported that sarcopenic visceral obesity is a phenotype that seems to be linked to inflammation, higher risk of fractures, and worse metabolic pattern. SO is associated with increased levels of serum hs-CRP among males,[58] and an increase in MCP-1 levels in the serum indicates a pro-inflammatory state. SO is linked to several loci, including those in the protein tyrosine phosphatase receptor type D(PTPRD), cyclin-dependent kinase 14 (CDK14), and inner mitochondrial membrane peptidase 2-like (IMMP2L) genes.[7] Pro-inflammatory cytokines, including TNF-α, IL-6, IL-1, MCP-1, and fetuin-A (FetA), are secreted more frequently when there is an increase in fat tissue or when macrophages invade adipocytes.[59] Additionally, adipokines that induce lipotoxicity in skeletal muscle cells are produced by adipose tissue, which contributes to the pathophysiology of sarcopenia.[139] An imbalance between pro-inflammatory adipokines and anti-inflammatory myokines is caused by the transition of adipose tissue from subcutaneous to visceral adipose sites, as well as skeletal muscle atrophy during the aging process.[140] Furthermore, as people age, their adipocyte hormone leptin production increases, which can result in resistance to leptin, impaired fatty acid oxidation in the muscles, ectopic fat deposition in these tissues, and muscular atrophy.[60,61]

Dynamic Nature of Weight-Metabolic Phenotypes

The dynamic and ever-changing characteristics of metabolic weight phenotypes make it difficult to predict outcomes. An individual's health state can transition from metabolically healthy to metabolically unhealthy, for example, from NWO to MONW or MHO to MAO. MHO, NWO, MUO, and MONW may transform into SO as people age. A third to 50% of individuals with MHO eventually reach an unhealthy metabolic state.[61,141–143] Additionally, these results imply that metabolic phenotypes of weight are dynamic phenomena that need to be monitored over time.

Overweight or Obese and MAFLD

Given the worldwide epidemic incidence of MAFLD[144] and obesity,[145] it is necessary to clarify the pathophysiological relationship between these two conditions[146] [Table 2]. The cliche "fat people have fatty livers" does not explain how anything comes about.

Association Between MHO and MAFLD

Currently, there is no understanding of how MHO affects MAFLD risk. However, according to recent epidemiological research, MHO can be significantly linked to a higher chance of developing MAFLD.[62,63,147] For instance, a study of 270 individuals with MHO who underwent bariatric surgery found that 35.5% (96/270) of obese individuals had NAFLD, 8.2% (22/270) had NASH, and 4.4% (12/270) had liver fibrosis.[62] Sung et al found that 45% of MHO individuals had ultrasonically defined MAFLD in a large cohort survey of South Koreans.[63] Chang et al discovered that an increase in BMI was independently related to an increased incidence of MAFLD at a mean follow-up of 4.5 years in a cohort of 77,425 South Koreans who were metabolically healthy and free from MAFLD at baseline.[147]

Association Between MUO and MAFLD

Approximately 90%-95% of individuals with extreme obesity and associated MetS characteristics have imaging-defined MAFLD, and more than a third of these patients develop histological NASH.[64] Increased BMI and waist measurements are linked not only to MAFLD, but also to a higher risk of liver disease progression, especially in elderly individuals.[148] This may be due in part to the fact that visceral fat has a stronger correlation with MAFLD than subcutaneous fat does.[31] Visceral adipose tissue differs from subcutaneous fat in that it releases more pro-inflammatory and pro-fibrogenic mediators, has greater lipolytic rates, and is associated with increased insulin resistance. These factors may contribute to MAFLD development and progression.[31] All of these processes have demonstrated that one of the most significant risk factors for developing more severe types of MAFLD is the presence of expanded and inflamed (dysfunctional)visceral adipose tissue.[68,69] Patients with "cryptogenic" cirrhosis also frequently exhibit MetS characteristics, indicating that "burned-out" NASH may account for the majority of these instances.[65]

The Correlation Factors to MUO and MAFLD

In addition to aggravating liver/systemic insulin resistance and predisposing to dyslipidemia, MAFLD releases several pro-inflammatory and vasoactive mediators that may facilitate the emergence of cardiometabolic problems linked to obesity.[2,66,67] Individuals who are fat may acquire metabolic irregularities as a result of certain foods. For instance, in obese individuals, dietary fructose intake promotes de novo lipogenesis, encourages atherogenic dyslipidemia, exacerbates IR, and increases visceral adiposity.[70] Drinking sweetened drinks increases the risk of MAFLD in overweight or obese individuals[71] Cardio-respiratory fitness and MAFLD are connected to one another.[72] According to Argo et al,[149] patients with NASH have aerobic power and capacity comparable to that of sedentary control subjects.

Elevated serum uric acid (SUA) levels are a novel risk factor for MAFLD.[73] 10,000 Chinese people participated in the study by Zhang et al showed that obesity and high SUA levels both enhance the risk of MAFLD and hypertriglyceridemia.[150] There is evidence that some genetic variants associated with MAFLD interact with obesity. In particular, a significant interaction effect between the polymorphism patatin-like phospholipase domain-containing protein 3 (PNPLA3) rs738409 and obesity was identified.[28,74,151] A worldwide cohort study by Stender et al revealed that PNPLA3 G/G genotype carriers had a risk of cirrhosis that was roughly six times greater if they were obese compared to PNPLA3 C/G or C/C genotypes.[74]

MAFLD and the Dynamic Change from MHO to MUO

In MHO and MUO patients during a median follow-up of 7.7 years, Kim et al observed that BMI was independently associated with deteriorating liver fibrosis. They also discovered that 70% of those with MHO developed MUO during follow-up, indicating that their metabolic health status was not static.[152] NASH and severe fibrosis appear to be substantially less common in patients with MHO than in those with MAO.[153,154] Collectively, the available data indicate that patients with MHO are more likely to develop MAFLD and liver disease than individuals with normal weight who are metabolically healthy(NWMH). However, this risk is often lower than that in MUO patients. A significant effort should be made to discover MAFLD in all obese individuals since MHO is not a stable condition, and MAFLD can predict the shift from MHO to MUO [Figure 1].

The Sarcopenia and MAFLD

The prevalence of sarcopenia in individuals with MAFLD ranges from 12.2% to 43.6%, which is substantially greater than that in patients without MAFLD, which ranges from 8% to 9.7%.[75] Skeletal muscle mass was negatively linked with the occurrence of MAFLD[155,156] and positively associated with MAFLD resolution in two retrospective cohort investigations.[156] The degree of steatosis or fibrosis associated with MAFLD and sarcopenia was independently correlated according to further cross-sectional and retrospective investigations.[157–159] A greater risk of developing severe MAFLD was linked to reduced muscle mass and grip strength in another prospective trial with a 10-year median follow-up period.[160]

The SO and MAFLD have been used in several studies. In a retrospective multicenter study involving MAFLD participants, the frequency of SO was 5.4% (1297/23,889).[76] Compared to the two components (sarcopenia and obesity) alone, surrogate indicators of sarcopenic obesity were separately linked to a greater risk of NAFLD,[77–79] NASH,[77,78] and severe fibrosis.[77,79] Chun et al[76] validated a model of high-risk and low-risk SO, and discovered that high-risk individuals had a markedly increased risk of severe hepatic fibrosis or atherosclerotic cardiovascular disease (ASCVD). After a median follow-up of three years, high-risk individuals had significantly higher cumulative incidences of significant liver fibrosis, CVD, cirrhosis, and all-cause mortality.[76]

Normal-Weight and MAFLD

A significant portion of all MAFLD cases worldwide, between 10% and 20%, occur in the normal-weight population.[161] The so-called "lean" form of MAFLD (BMI within the ethnicity limit of 25 kg/m^2 for Caucasian individuals and 23 kg/m^2 for Asian subjects) can manifest even in the absence of obesity. With the exception of liver steatosis caused by a monogenic illness, the majority of lean MAFLD patients have visceral adiposity and insulin resistance, but a normal BMI. These patients may be lean at BMI thresholds, but obese based on waist circumference or other body composition measurements.[162] This subtype of MAFLD is likely caused by high calorie consumption, mainly from single carbohydrates, and a sedentary lifestyle, which leads to liver steatosis and lipotoxicity. The pathophysiology of this MAFLD subtype is similar to that of overweight and obese individuals[163] [Table 2, Figure 1].

Epidemiology

According to epidemiological research, lean individuals with MAFLD are less likely to exhibit metabolic abnormalities than overweight or obese patients, and are more likely to be male, older, and have larger waist circumferences.[164] A prevalence of between 5% and 26% has been reported for MAFLD in individuals of normal weight, accounting for 15%-50% of all instances of the disease. For instance, a study of 810 Chinese adults with normal weight found that 17.5% had MAFLD.[165] Lean MAFLD was present in 5.1% of the general population and 19.2% of the world's MAFLD population, according to a meta-analysis of 93 different studies.[80] Overall, MAFLD prevalence among the normal-weight population was 12% in Asia, 10.2% in the Middle East, and 9.2% in Europe.[16]

Lean MAFLD Disease Severity and Long-Term Prognosis

Data on the long-term prognosis of MAFLD in a population with normal weight are scarce and conflicting. In comparison to obese and MAFLD patients, a study of Swedish MAFLD patients found a 2.69-fold increased chance of developing severe liver disease but no increase in mortality in MAFLD patients with normal weight.[166] Similar to other studies, which similarly found no difference in survival between patients with lean MAFLD and those without it.[167] According to a meta-analysis encompassing 35,707 individuals, patients with lean MAFLD had higher overall, liver-specific, and cardiovascular mortality than those with obesity and MAFLD.[80] Those with lean MAFLD had greater all-cause mortality than those with non-lean MAFLD.[81] According to a previous study, individuals with lean MAFLD had milder clinical events and prognoses than those with obesity and MAFLD, and they also experienced fewer cardiovascular events and fatalities.[82,83] MAFLD patients with normal weights had considerably lower rates of metabolic abnormalities, cirrhosis, and cardiovascular disease than non-lean participants.[84,85]

Multiple extrahepatic symptoms are associated with an elevated risk in patients with normal-weight MAFLD. Lean MAFLD was a substantial risk factor for incident T2DM over a 6-year follow-up median, according to a longitudinal study of 14,482 Chinese people without T2DM (p= 0.001).[168] Lean MAFLD individuals may have higher 15-year cumulative all-cause mortality, but there was no difference in cardiovascular or cancer-related mortality compared to obese MAFLD patients according to a real-world study of 4,711 MAFLD patients.[169] Additionally, a subanalysis showed that although it was lower than that in patients with non-lean MAFLD, patients with lean MAFLD had significantly higher all-cause (p=0.0002) and cardiovascular mortality (p=0.0004) than those with normal weight and without MAFLD.[170] The frequency of T2DM, hypertension, dyslipidemia, and CVD was shown in some other reports to be lower in patients with lean MAFLD than in those with non-lean MAFLD.[85,89] In conclusion, patients with lean MAFLD may have a similar prognosis to those with overweight or obese MAFLD in terms of long-term outcomes compared to healthy individuals.

Histological Characteristics

The metabolic profile of IR in the main target tissues (muscle, liver, and adipose tissue) was not different from that of the sample of 12 lean individuals with biopsy-proven MAFLD compared to obese patients.[171] The morphological characteristics of MAFLD in individuals of normal weight are thought to be indistinguishable from those of MAFLD.[89] Those with lean MAFLD had better histological and metabolic symptoms than those with obesity. According to a study of 1339 patients, patients with normal weight were histologically less severe. Compared to overweight individuals, obese patients had a reduced prevalence of T2DM (9.2% vs 31.4%), steatohepatitis (54.1% vs 71.2%), and advanced fibrosis (10.1% vs 25.2%).[167] According to a meta-analysis of eight studies involving 1,441 individuals, patients with lean MAFLD had significantly less pathological steatohepatitis (39% vs 52.9%) and significant fibrosis (29.2% vs 38.3%) than obese patients with MAFLD.[80] However, other cross-sectional investigations showed that patients with lean MAFLD had worse liver histology than those with non-lean MAFLD, with greater proportions of advanced fibrosis, blossoming, lobular inflammation, and steatohepatitis.[172,173]

The Risk Correlation to MUNW and Lean MAFLD

The proportion of patients with MUNW ranged from 21% to 43.6% in the multi-ethnic atherosclerotic investigation, while the prevalence of lean MAFLD (BMI<30 kg/m^2), as determined by computed tomography, was 11%.[174] The significant incidence of metabolic problems among lean MAFLD patients indicates that independent determinants of metabolic health may include food quality, in addition to overall calorie intake.[86] Determining metabolic health, for instance involves pro-inflammatory foods or eating habits with a strong pro-inflammatory profile.[36] Another study found that compared to healthy individuals of normal weight, those with metabolic obesity ingested more total energy, less fiber, lower levels of antioxidant chemicals, and fewer servings of fruit, legumes, nuts, and seeds.[87] Notably, patients with lean MAFLD have been shown to consume more cholesterol than those with obesity and MAFLD.[88] Higher dietary inflammatory index scores have been linked to inflammatory indicators in the serum, namely C-responsive proteins, according to several studies.[175] According to a microbiome study, individuals with lean MAFLD may have a microbiota that is more enriched than that of patients with obesity and MAFLD (such as *Erysipelotrichaceae* and *Clostridiales*), which is thought to contribute to the development of hepatic steatosis. There was a decrease in the *Marvinbryantia* and *Christensellenaceae R7* groups and an increase in the *Dorea spp* in the lean MAFLD group compared with healthy individuals of normal weight.[89]

Total Fat Mass and Regional Fat Accumulation

According to new research, the formation of a metabolically healthy phenotype versus an unhealthy phenotype is influenced by differences in total body fat and regional fat accumulation. Peripheral fat has a limited ability to store fat such as SAT, which has little metabolic impact. In the context of overeating, ectopic fat deposits in tissues, including the liver and skeletal muscle, increase the risk of CVD.[92] Ectopic fat is thought to be essential for the development of IR and lipotoxicity in humans, and is thought to have a more direct impact on the metabolic effects of obesity.[92] The distribution of body fat is likely governed by genetic factors, and numerous studies have discovered variants such as dendrocyte expressed seven transmembrane protein domain-containing 2 (DCST2) rs905938 and the golgin RAB6-interacting (GORAB) rs10919388.[90,91] When compared to the healthy range, genome-wide association studies (GWAS) of up to 188,577 individuals found 53 loci [such as lethal(3)malignant brain tumor-like protein 3 (L3MBTL3), dynein axonemal heavy chain 10 (DNAH10), and coiled-coil domain containing 92 (CCDC92)] that were associated with a higher risk of cardiometabolic disease, lower peripheral fat, and increased IR (higher fasting insulin, higher triglyceride levels, and lower HDL cholesterol levels).[92] Other research have identified advantageous fat genes [(such as peroxisome proliferator-activated receptor gamma (PPARG) and lysophospholipase-like 1 (LYPLAL1)] that are linked to increased SAT but a decreased risk of heart disease, T2DM, liver fat, and hypertension.[176,177]

Pathophysiology of Lean MAFLD Genetic Contribution

The factors associated with lean MAFLD remain unknown despite the effectiveness of GWAS in identifying genetic loci linked to the risk of MAFLD development and progression.[178] Another study using whole-exome sequencing connected lean MAFLD to a phosphatidylethanolamine N-methyltransferase variety.[179] Other studies have linked the PNPLA3 risk allele to higher levels of fibrosis (stage 2 or greater) and the onset of steatohepatitis in patients with MAFLD of normal weight.[93,94] The transmembrane 6 superfamily member 2 (TM6SF2) gene showed increased rates of transport of rs58542926 C>T in studies comparing MAFLD patients with normal weight and obese patients.[95,96] Patients with normal weight had a significant independent correlation between the Interferon lambda 4(IFNL4) genotype rs368234815 TT allele and severe fibrosis (P=0.02) but not in obese patients (P=0.15).[97] Although understudied, the human epigenome offers crucial information for understanding the fundamentals of gene-environment interactions to clarify the pathophysiology of MAFLD in individuals of normal weight.

MAFLD and T2DM

Two pathologic diseases, MAFLD and T2DM, typically coexist and work in concert to increase the risk of unfavorable hepatic and extrahepatic outcomes[180,181] [Table 2, Figure 2]. According to a meta-analysis of observational research from 20 different countries, over 56% of individuals with T2DM worldwide have MAFLD.[98] T2DM is also known to increase the risk of NAFLD, progressing more quickly to cirrhosis, NASH, or hepatocellular carcinoma (HCC). However, the association between NAFLD and T2DM is more complicated than previously believed and appears to be bilateral.[66,182] Indeed, increasing evidence suggests that NAFLD could lead to and/or encourage the development of T2DM and that the likelihood of acquiring T2DM correlates with the severity of NAFLD.[183] Given the same Pathobiology of T2DM and MAFLD, both conditions coexist in many patients and may worsen the outcomes of underlying diseases with accelerated development and higher comorbidities.[184]

MAFLD is Predictive of T2DM

Numerous cohort studies conducted over the past ten years have consistently demonstrated that MAFLD can predict incident T2DM. A meta-analysis involving 501,022 people found that MAFLD was linked to a doubling of the chance of developing T2DM and that this risk seemed to increase as hepatic steatosis and fibrosis severity increased.[185] Morrison et al supported the idea that there is a causal relationship between MAFLD and T2DM by confirming that individuals with MAFLD have a higher chance of developing T2DM than those without it.[186]

Is the increased risk of T2DM caused by MAFLD present only in patients with advanced MAFLD, or does it affect all MAFLD patients? The magnitude of T2DM risk is clearly correlated with the severity of MAFLD and specifically the severity of liver fibrosis, according to recent data from a complete meta-analysis.[185] In particular, a retrospective cohort analysis of 396 Swedish MAFLD patients found that during the course of a mean follow-up of 18.4 years, more patients with fibrosis stage 3 than those with fibrosis stages 0–2 (51% versus 31%) acquired incident T2DM.[99] It is important to note that a rising amount of steatosis was likewise connected to the T2DM event in patients with 0–2 fibrosis.[99] In a different cohort study of 129 Swedish individuals with MAFLD, Nasr et al Incident T2DM occurred in 69 patients (53.5% of the total), and this risk was significantly higher in those who developed fibrosis over time.[187] The authors demonstrated that liver fat levels predicted the likelihood of T2DM in the same group.[188] Additionally, there was a link between a lower risk of T2DM and decreased liver fat between the baseline and the first follow-up.[188] According to a number of observational cohort studies, temporal variations in MAFLD status of MAFLD were linked to significantly varied T2DM risks. More importantly, regardless of changes in body weight, the likelihood of a T2DM event seemed to diminish over time when MAFLD was improved or resolved.[189–191] For instance, over a five-year period, independent of known risk variables, a significant decline in the probability of T2DM was observed in subjects with reduced liver steatosis.[192]

Cluster Analysis of the Genotyping Array Study

Cluster analysis of the German Diabetes Study revealed that the subtype of diabetes is more likely to be insulin-resistant, and to a lesser extent, that particular subtypes associated with obesity and age showed noticeably greater levels of liver fat and noninvasive fibrosis biomarkers upon diagnosis of T2DM.[193] This discovery emphasizes the significance of the interplay between IR and lipid metabolism in the liver during T2DM onset. The rs738409(G) polymorphism of PNPLA3 was more common in the severe insulin-resistant diabetes subtype, and this genetic variation was also associated with higher IR in adipose tissue.[193,194] Mendelian randomization studies have provided additional evidence that genetically induced MAFLD increases the risk of developing insulin resistance and new-onset T2DM (PNPLA3, TM6SF2, and other MAFLD-related genetic variations).[28,100,101] Increased levels of hepatic fat are linked to an increased risk of incident T2DM according to a significant exam-based genotyping study.[151]

Mechanisms Linking MAFLD and T2DM

The specific aspects of MAFLD that increase the risk of T2DM are unclear. However, it is widely known that lipid accumulation in the liver is associated with both hepatic IR and inflammation, both of which are important aspects of MAFLD. Therefore, interventions that improve IR and chronic inflammation in MAFLD may help to lower the risk of T2DM by reducing hepatic lipid accumulation. [Figure 2] The most prevalent plasma lipid abnormality in MAFLD is atherogenic dyslipidemia, which is often characterized by elevated levels of very low-density lipoprotein (VLDL), small dense LDLs, and decreased levels of HDL cholesterol.[102] The levels of VLDL1-triglycerides and VLDL1-palmitic acid increased more in individuals whose diabetes (which had been put into remission by weight loss) relapsed than in those whose diabetes did not relapse, which is an intriguing finding that suggests that the increase in VLDL may further enhance the risk of T2DM with MAFLD.[195] Additionally, these individuals had higher intra-pancreatic fat levels and no longer responded to glucose challenge with first-phase insulin.[195] It is not certain, nevertheless, that variations in VLDLs linked to MAFLD directly affect the incidence of T2DM.

As previously mentioned, throughout the spectrum of liver disease in MAFLD, an elevated risk of T2DM appears to occur early (with fat accumulation in the liver) and late (with inflammation and liver fibrosis). Strong data to date point to an increased risk of T2DM and hepatic, adipose tissue, and muscle insulin resistance related to the accumulation of lipids in the liver [Figure 2].[180,192,196] To further support this notion, a decline in liver lipid accumulation has also been linked to a lower likelihood of developing T2DM.[192] A number of mechanisms have been proposed, including those linked to increased liver lipid accumulation, such as dietary components (for example, saturated fat and carbohydrate intake), changes in gut microbiota, and elements related to intestinal function (for example, bile acid metabolism, levels of lipopolysaccharide and incretins, or altered intestinal permeability).[16] However, the precise factors of MAFLD that may increase the risk of T2DM remain unknown. Factors associated with the accumulation of lipid metabolites in the liver, mitochondrial oxidative capacity, and lipoprotein secretion are anticipated to negatively impact T2DM risk in the early stages of liver disease. However, variables including lipid metabolites, pro-inflammatory cytokines, and hepatochemicals are most likely to be important pathogenic factors in the latter stages of liver disease, when the liver has already begun to swell and develop fibrosis[196,197] [Figure 2].

The Treatment for Obesity and MAFLD

In general, attempts to reduce weight through food and exercise result in 30% of patients losing more than 5% of their total body weight loss (TBWL) within 6 to 12 months.[198] However, the effectiveness of intensive lifestyle interventions has been limited. The use of second-level therapies for treating obesity, such as anti-obesity pharmacotherapy, bariatric endoscopy, and surgery for all patients with obesity or obesity-related comorbidities who do not successfully lose weight through lifestyle changes alone, must be increased to achieve meaningful weight loss and prevent weight regain[199] [Table 3].

Lifestyle Modifications

Changes in lifestyle, including food intake, activity, exercise, and weight loss, are the main treatments for MAFLD.[200,201] According to several studies, weight loss in MAFLD patients reduces liver triglyceride and NAS levels while lowering cardiovascular risk markers such as IR and serum lipid concentration.[104] Musso et al found that a weight loss of 7% resulted in significant improvements in histological results and cardiometabolic profile; therefore, it is advised that the weight loss objective for NASH should be close to 10%.[202] Vilar-Gomez et al also discovered that weight loss improved the NASH-related histological parameters and was an independent factor ($p<0.01$).[203] A Meta by Haigh found that the degree of calorie restriction had a dose-response relationship with favorable effects on liver function and weight reduction, indicating that this strategy should continue to be the cornerstone of MAFLD diet treatment.[103] Ryan et al investigated the impact of the Mediterranean diet (Med Diet) in comparison to a low-fat, high-carbohydrate diet (LF-HCD) and discovered that while there was no significant difference in weight reduction between the two dietary groups, there was a substantial difference in MAFLD and insulin sensitivity.[105]

A thorough lifestyle intervention program should include increasing aerobic physical activity by 150 min each week, in addition to a diet with fewer calories. With a target of more than 10,000 steps per day (as fast walking for 30 min each day on most days of the week). In the long term (more than a year), higher amounts of physical activity between 200 and 300 minutes per week are advised to sustain weight loss or prevent weight gain.[106] Recommendations for diet and exercise offer well-structured behavioral techniques to help with diet and exercise compliance.[204]

Anti-Obesity Pharmacotherapy

The Food and Drug Administration (FDA) approved Anti-obesity medications (AOMs) for use in patients with a body mass index (BMI) >30 kg/m^2 or those with a BMI >27 kg/m^2 and one or more obesity-related comorbidities such as T2DM, hypertension, and dyslipidemia as the next line of treatment for obesity or obesity-related liver diseases.[205] AMOs currently approved for long-term use include Bupropion/naltrexone, Orlistat, Liraglutide, Semaglutide, and Phentermine/topiramate.[206] However, only Orlistat and Liraglutide have been thoroughly investigated for liver illness.

Clinical investigations have included a wide range of novel therapeutic targets and prospective medications for the treatment of obesity and MAFLD; however, the results and efficacy have not yet been validated.[207–210]

Glucagon-like peptide-1 (GLP-1)is an incretin hormone that originates from the gut. Additionally, it reduces caloric intake and stomach emptying while increasing insulin release through beta cells. According to one study, liraglutide completely resolved NASH without increasing fibrosis, and improved steatosis.[107] GLP-1 analogs increase insulin sensitivity and decrease body weight. A similar long-acting GLP-1 receptor agonist, semiglutide, demonstrated a substantial decrease in average body weight and improvement in NASH in a double-blind randomized controlled trial (RCT); however, the improvement in fibrosis stage was not significant.[108] These results support the use of Liraglutide or other GLP-1 mimics as desirable medications for patients with NASH.

By establishing covalent connections with serum residues from active lipase sites, orlistat locally inhibits stomach and pancreatic lipases, rendering them inactive. The use of orlistat improved all liver enzymes (ALT and AST) and liver fat content (LFC) based on liver histology, according to numerous studies that examined the impact of orlistat use and dietary changes on MAFLD.[199] Both the absolute drop in LFC in the Orlistat group and the experimental diet group were higher than those in the control group ($P<0.05$), at 9.1% and 5.4%, respectively.[110] One review, which included 330 individuals with NAFLD or NASH, discovered that orlistat improved the levels of ALT, AST, gamma-glutamyl transferase (GGT), glucose, triglycerides, HOMA-IR, and BMI, but not the liver fibrosis score (SMD=−0.14; P=0.7). Patients with NASH showed no discernible changes in the subanalyses of various patient categories.[111] However, no statistically significant difference in weight loss was identified between the orlistat/diet/vitamin E group and diet/vitamin E group in a RCT conducted by Harrison et al to evaluate the effectiveness of 120 mg of orlistat three times a day (TID) in treating NASH in patients, which suggests that orlistat improvement in MAFLD could be a result of weight reduction.[109]

Bariatric Endoscopic Interventions

Endoscopic bariatric therapy (EBT), a recently developed safe alternative to more invasive and traditional bariatric operations, helps patients lose weight, especially those with mild to moderate obesity (BMI of 30–40 kg/m^2) who do not have comorbid conditions and have tried unsuccessfully to lose weight through lifestyle and medication changes.[211] Theoretically, EBT may be among the safest, least intrusive, and most efficient treatments for MAFLD.

Intragastric balloon (IGB) is an endoscopic space occupancy procedure that promotes weight loss by decreasing the feeling of hunger before meals, enhancing satiety in the stomach, and delaying gastric emptying to improve postprandial satiety.[112] Apollo Endosurgery was granted permission by the US FDA to utilize Orbera in the treatment of patients with a BMI between 30 and 40 kg/m^2 and non-cirrhotic NASH with hepatic fibrosis in March 2021.[212] In 21 patients with MAFLD, Bazerbachi et al evaluated the impact of single-fluid-filled IGB on the metabolic and histological features of NASH. After six months of IGB, the median initial TBWL was 11.7%, and the mean NAFLD Activity Score (NAS) considerably improved in 90% of patients (18/20), with a median decrease of 3 points, and 15% of participants experienced liver regression in fibrosis at 1.17 stages.[113] Another meta-analysis also found an average reduction in participant body weight of 11.9 kg, with a significant histological improvement (p=0.03) in the NAS.[114] Additionally, a systematic study by Candlean et al revealed that 83.5% of patients' NAS improved, while 79.2% of patients' steatosis improved.[115] These findings point to a bright future for the use of IGB in the treatment of NASH and MAFLD.

Endoscopic gastroplasty (ESG) is a minimally invasive bariatric endoscopic technique that involves reshaping of the greater curvature without making an incision.[116] ESG not only achieves substantial weight loss but also has strong potential to improve MAFLD and steatohepatitis. In a study of 118 ESG patients with liver steatosis, Hajifathalian et al discovered a significant reduction in NAS (p=0.034), and 20% of the patients had liver fibrosis stage F3-F4 to F0-F2 (p=0.02).[117]

The duodenum is considered the target organ for weight loss. By modifying, eliminating, or omitting duodenal exposure to intraluminal nutrients, favorable metabolic effects were observed.[118] The process known as endoscopic duodenal mucosal resurfacing (DMR) is regarded as being minimally invasive. Oliveira et al performed a meta-analysis to investigate the effectiveness of DMR in metabolic enhancement. After three months of DMR, Glycosylated Hemoglobin, Type A1C (HbA1C) levels dramatically decreased by 1.72% (p=0.02), and the average weight decreased by 3.1 kg ($p<0.001$). Liver enzymes (ALT) and liver steatosis visible on magnetic resonance imaging(MRI) were both dramatically decreased ($p<0.001$).[119] These results lend credence to the effectiveness of the DMR method in resolving

MAFLD. This may indicate a different mechanism by which the duodenal mucosa and released incretine hormones contribute to the onset of MAFLD.

Bariatric Surgical Intervention

Many studies have been conducted on how bariatric and metabolic surgeries affect long-term weight loss and improve obesity-related comorbidities.[213] Patients with a severe BMI of 40 kg/m^2 or 35 kg/m^2 and obesity-related comorbidities should undergo these procedures.[199] According to a long-term prospective study, at the 5-year follow-up, fibrosis regressed in 70% of patients ($p<0.001$) and resolved in 84% of patients with NASH due to bariatric surgery ($p<0.001$).[214]

Restrictive bariatric treatment, known as sleeve gastrectomy (SG), entails resecting two-thirds of the stomach's larger curvature and creating a long tubular gastric duct along the lower curvature.[120] When compared with Roux-en-Y Gastric Bypass (RYGB), Baldwin et al discovered that patients who underwent SG showed a substantial reduction in NAS of 2.3 ($p<0.00001$). Regarding NAFLD Fibrosis Score (NFS) reduction, there was a statistically significant difference between the two methods ($p<0.00001$): LSG had a mean reduction of 0.7 ($p=0.07$), whereas RYGB had a decrease of 1.0.[121] In a prospective study of 94 obese participants, SG caused statistically significant weight loss and a substantial decrease in BMI from 44. 54±5. 45 kg/m^2 to 34. 23±2. 66 kg/m^2 ($p< 0.001$) in the first year following surgery. In addition, the NAS score dramatically decreased over the course of a year, falling from 5.2±1. 96 to 2.63±1.55.[122] These results confirmed the effectiveness of SG in managing obesity complicated by MAFLD.

Surgery called the Roux-en-Y Gastric Bypass (RYGB) has both malabsorptive and restrictive effects. By joining a section of the small intestine to a smaller stomach pouch in the shape of the letter "Y", it is regarded as a gastrointestinal reconstruction technique.[123] According to Fakhry et al, 91, 60, and 31% of all RYGB candidates had improved or fully resolved steatosis, steatohepatitis, and fibrosis, respectively.[215] Baldwins et al's meta-analysis revealed that after RYGB surgery, the NAS and NFS were significantly reduced by −2.8 ($p<0.00001$) and −1.0 ($p<0.00001$), respectively.[121] In contrast, there was little difference between RYGB and SG in the head-to-head comparison of NAS, preferring RYGB outcomes. Overall, their research found that there was no clear advantage between the two types of operations and that both RYGB and SG had a favorable effect on the liver profile.[121]

Conclusion

Compared to MAFLD, which develops in the context of overweight and obesity, some individuals are normal weight, or have T2DM. There are many unknowns in our understanding of disease progression. The answers to these questions will inform the development and mapping of effective preventive and therapeutic approaches for people with metabolic comorbidities. Since obesity and IR are correlated with MAFLD, this review shows a wide range of metabolic phenotypes of obesity, which are more likely to distinguish different types of MAFLD depending on patient characteristics.

This review provides a systematic introduction to the treatment of obesity and MAFLD. It includes diet, exercise, drugs for obesity, and endoscopic and surgical bariatric procedures. Drugs and Bariatric procedures provide more lasting weight loss, which was evident in some improvements in the MAFLD activity score and fibrosis. Although further research is needed to draw a definitive conclusion, the data presented above have significant implications for public health and clinical practice decision-making. This highlights the urgent need to develop effective treatments for MAFLD to reduce the risk of comorbidities and extra-liver complications.

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